

## Aberystwyth University

### *Constraint-based optimisation tools for semi-automated refinement of genome-scale yeast metabolic models*

Pir, Pinar; Dobson, Paul D.; Smallbone, Kieran; Mendes, Pedro; King, Ross Donald; Lu, Chuan; Oliver, Stephen G.; Clare, Amanda

*Publication date:*  
2010

*Citation for published version (APA):*

Pir, P., Dobson, P. D., Smallbone, K., Mendes, P., King, R. D., Lu, C., Oliver, S. G., & Clare, A. (2010).

*Constraint-based optimisation tools for semi-automated refinement of genome-scale yeast metabolic models.*  
<http://hdl.handle.net/2160/5847>

#### **General rights**

Copyright and moral rights for the publications made accessible in the Aberystwyth Research Portal (the Institutional Repository) are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Aberystwyth Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Aberystwyth Research Portal

#### **Take down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

tel: +44 1970 62 2400  
email: [is@aber.ac.uk](mailto:is@aber.ac.uk)

# Constraint-based Optimisation Tools for Semi-automated Refinement of Genome-scale Yeast Metabolic Models

Chuan Lu<sup>1</sup> Pinar Pir<sup>2</sup>, Kieran Smallbone<sup>3</sup>, Paul D. Dobson<sup>4</sup>, Amanda Clare<sup>1</sup>,

Pedro Mendes<sup>3</sup>, Stephen G. Oliver<sup>2</sup>, and Ross D. King<sup>1</sup>,

<sup>1</sup>Department of Computer Science, Aberystwyth University, UK, <sup>2</sup>Cambridge Systems Biology Centre, Department of Biochemistry, University of Cambridge, UK,

<sup>3</sup>Manchester Centre for Integrative Systems Biology, University of Manchester, UK, <sup>4</sup>School of Chemistry, University of Manchester, UK

## Introduction

### Motivation

- Genome-scale metabolic network models are useful for analysing the cellular behaviour of organisms
- Semi-automated procedure for model validation and refinement are important for quality assurance in such models
- Computational tools for iterative model validation and optimisation are necessary to assist hypothesis generation and evaluation

### Genome scale metabolic models for *S. cerevisiae*

- A consensus reconstruction: Yeast1, community driven, rigorously evidenced, well annotated [1]
- Further development: Yeast4, expanded from Yeast1, with improved representation of metabolic transport, lipid metabolism, etc. [2]
- Yeast4: 1102 unique metabolite reactions, and 924 metabolites located in 15 cellular compartments

## Applications

### Computational tool implementation

- Implemented in Python, using CPLEX, glpk, IpSolve as LP/MILP solvers
- Read/write models in SBML format
  - Model stored in bipartite graph and/or stoichiometry matrices
  - Suitable for both FBA and logical model simulations
- Converting model network (bi-level) optimisation problem to constraint-based optimisation problem: LP, MILP.
- Algorithms for gap filling, OMNI
- Search algorithms for graph traverse, and identification of minimal models

### Model validation with experimental data

- Single deletion data under minimal medium
- Wildtype growing under different conditions: RobotScientist's [3] automated titration experiments on yeast utilising amino acids as sole C/N source
- Awareness of data quality issue

## Methods

### Framework of Flux Balance Analysis (FBA)

- Identification of flux distribution using stoichiometry model, assuming steady states, with constraints on mass balance and thermodynamics to maximise/minimise an objective function (e.g. to max growth rate)
- Utilisation of constraint-based optimisation, linear/nonlinear programming (LP/NLP), mixed integer linear programming (MILP)

### Gap filling

- Structural Gaps in metabolic networks
  - Reaction gaps, missing gene-protein-reaction associations, etc.
- Mechanisms to rescue reaction gaps
  - Reversibility; transport; biomass formation; metabolite exchange
  - Addition of missing reactions from reference model
- Identification of minimal set of reactions to add on, in order to restore biomass formation or blocked reactions [4]

### Optimal Metabolic Network Identification (OMNI)

- Models under-constrained:
  - Reactions absent in yeast, irreversible or unfavorable under certain conditions, suppressed due to regulatory, etc.
- Bi-level constrained optimisation:
  - Minimisation of discrepancies between observations and predictions while maximising the growth rate [5]
  - Converting to MILP by exploiting duality for LP

### Gap filling procedure

- Constraint-based optimisation and literature searching
- Solutions for 14 of 16 false inviable single deletions under minimal medium
- Further curation needed to fill in the missing reaction esp. for alternative pathways of ergosterol biosynthesis

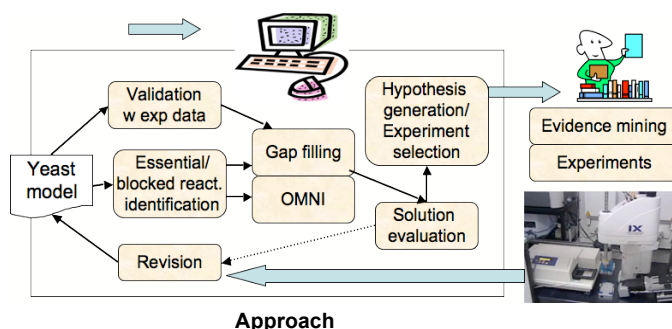
Single deletant	Non-productive biomass comp.	Revision suggestions	Revision field	Reference
IPT1, CSG2, PXA2, PXA1	MIP2C	Remove MIP2C from biomass, not essential for cell growth.	Biomass formation	PIMD: 9368028
SLC1	phosphatidylcholine triglyceride,...	1-acyl-sn-glycerol-3-phosphate acyltransferase: SLC1 => SLC4.	GPR	PIMD: 17726007
ILV6	L-valine, L-isoleucine	2-aceto-2-hydroxybutanoate synthase and acetolactate synthase: ILV6: ILV2 => ILV6: ILV2 JLV2.	GPR	PMID: 10213630
TGL2	triglyceride	Adding 2 putative transport reactions between cytosol and lipid particle.	Transport reaction	Gap filling algorithm
...	...	...	...	...

### OMNI procedure

- More than 1 solution for 12 out of 48 false viable cases subject to OMNI
- Solution evaluation: *in-silico* simulation using phenotype data in SGD
- Application of a minimal set of revisions, resulting in:
  - True inviables increased by 12, at the cost of 1 extra false inviable
- Suggested revisions:
  - Constraining the reaction directionality
  - Removing reactions:
    - e.g. alternative pathway for quinolinate synthesis absent in yeast
    - Adding regulator rules to control reaction activation e.g. GALT and GALE activated only after sensing galactose
  - Testing in vivo by robot: auxotrophy experiments

## Conclusions

- Proposed computational tools can **effectively search for (multiple) revision suggestions** for yeast metabolic models
- Semi-automated model refinement, supported with literature search and robot scientist experiments, helps to **improve the model in phenotype prediction**
- Future work**
  - Use of **logic programming** to integrate models with evidence from experimental data and constraint-based analysis
  - Learning GPR associations and regulatory rules and automated suggestion of experiments, either *in-silico* or *in-vivo***



**Acknowledgement**  
The EU FP7 project of UNICELLSYS

**Further information**  
Chuan Lu, PhD  
Dept. of Computer Science  
Aberystwyth University  
Aberystwyth  
SY23 3DB, Wales, UK  
cul@aber.ac.uk

### References

- Herrgård et al. A consensus yeast metabolic reconstruction obtained from a community approach to systems biology, Nature Biotechnol. 2008, 26
- Dobson et al. Further developments towards a genome-scale metabolic model of yeast. BMC Syst Biol, in press.
- King et al. The Automation of Science. Science 324(5923), 2009
- Reed et al. Systems approach to refining genome annotation. PNAS, 103:46, 2004.
- Herrgård et al. Identification of genome-scale metabolic network models using experimentally measured flux profiles. PLoS Comput Biol. 2006;2(7)